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The Gene Responsible for a Severe Form of Peripheral Neuropathy and Agenesis of the Corpus Callosum Maps to Chromosome 15q

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Summary

Peripheral neuropathy with or without agenesis of the corpus callosum (ACCPN) is a devastating neurodegenerative disorder that is transmitted as an autosomal recessive trait. Genealogical studies in a large number of affected French Canadian individuals suggest that ACCPN results from a single founder mutation. A genomewide search using 120 microsatellite DNA markers in 14 French Canadian families allowed the mapping of the ACCPN gene to a 5-cM region on chromosome 15q13-q15 that is flanked by markers D15S1040 and D15S118. A maximum two-point LOD score of 11.1 was obtained with the marker D15S971 at a recombination fraction of 0. Haplotype analysis and linkage disequilibrium support a founder effect. These findings are the first step in the identification of the gene responsible for ACCPN, which may shed some light on the numerous conditions associated with progressive peripheral neuropathy or agenesis of the corpus callosum.

Introduction

Peripheral neuropathy with or without agenesis of the corpus callosum (ACCPN), or Andermann syndrome (MIM 218000), is an autosomal recessive disorder that occurs with a high prevalence in the French Canadian population in the Charlevoix and Saguenay-Lac St Jean regions of the province of Quebec (Andermann et al. 1979, 1994; Andermann 1981). The clinical manifestations of ACCPN reflect a progressive peripheral neuropathy caused by axonal degeneration (Larbrisseau et al. 1984) and a CNS malformation characterized by absence or hypoplasia of the corpus callosum (Mathieu et al. 1990). The disease appears early in life, with delay in developmental milestones, areflexia, striking dysmorphic features, and mental retardation (Andermann et al. 1972; Andermann and Andermann 1994). Later in life, there is deterioration in motor ability, and hallucinatory psychosis often develops, suggesting progression of the CNS involvement as well (Filteau et al. 1991). The diagnosis of ACCPN is confirmed by muscle and nerve biopsies demonstrating muscle denervation and an axonal neuropathy with secondary demyelination (Larbrisseau et al. 1984) and by neuroimaging showing partial or complete agenesis of the corpus callosum (Mathieu et al. 1990). ACCPN is a progressive disorder, with death occurring typically in the 3d decade of life.

The incidence of ACCPN in Saguenay is 1/2,117 live births, and therefore the carrier frequency is estimated to be 1/23 (De Braekeleer et al. 1993). In contrast, only a small number of isolated cases of ACCPN have been described outside Quebec (Battistella et al. 1986; Renault et al. 1991; Hauser et al. 1993). It is believed that a founder effect is responsible for the high frequency of ACCPN in the French Canadian population, whereby a single mutation from an ancestral couple entered the gene pool and was distributed in the population over many generations (Andermann et al. 1979; Jetté et al. 1991). To date, no genetic evidence has been accumulated to support this claim. The goal of this study was to localize the ACCPN gene by linkage analysis and to confirm the founder-effect hypothesis.

Subjects, Material, and Methods

Pedigree Information

Fourteen pedigrees were selected for genetic linkage analysis and include both simple nuclear and multinuclear families from the Charlevoix and Saguenay-Lac St Jean regions. In total, 132 individuals participated, including 33 with ACCPN. Selection of families was based on the criteria of a thorough neurological evaluation confirming a clinical diagnosis of ACCPN. Each nuclear family consists of one to three affected offspring

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Table 1

Allele Sizes and Frequencies, Determined for the Five Markers in the Refined ACCPN Candidate Region, Based on a Control Group of 72–76 Normal Chromosomes from Unrelated French Canadians

	D15S1040		D15S971		D15S118		D15S1012		D15S214	
ALLELE	Size (bp)	Frequency	Size (bp)	Frequency	Size (bp)	Frequency	Size (bp)	Frequency	Size (bp)	Frequency
1	180	.01	191	.01	202	.04	145	.20	246	.03
2	182	.05	192	.03	204	.27	149	.22	252	.57
3	184	.35	194	.18	206	.18	151	.32	254	.01
4	186	.15	196	.19	208	.04	153	.01	258	.31
5	188	.07	198	.07	210	.01	155	.19	260	.07
6	190	.22	200	.11	212	.22	157	.05	262	.01
7	192	.03	202	.35	214	.20	159	.01		
8	194	.09	204	.06	216	.03				
9	196	.03			218	.01				

and from one to five unaffected offspring, and multinuclear families have between three and six affected individuals in the whole pedigree. There are known distant connections between ACCPN-1 and ACCPN-14, as well as between ACCPN-8 and ACCPN-12, although the four were considered independently in the linkage analysis. In addition, 12 unrelated single ACCPN patients were assessed and genotyped for the allelic-association analysis.

Molecular Analysis

DNA was extracted from blood samples (Maniatis et al. 1982) or lymphoblastoid cell lines (Anderson and Gusella 1984) from each individual. Dinucleotide $(CA)_n$ repeat polymorphic markers with high ($\geq$70%) heterozygosity from the 1993–94 Généthon map (Gyapay et al. 1994) were examined throughout the genome, to establish the chromosomal region linked to ACCPN.

Amplification of microsatellite fragments was accomplished by PCR. The reaction mixture was prepared in a total volume of 13 μl, by use of 80 ng of genomic DNA; 1.25 μl of 10 × buffer with 1.5 mM $MgCl_2$; 0.65 μl of BSA (2.0 mg/ml); 100 ng of each oligonucleotide primer; 200 mM each of dCTP, dGTP, and dTTP; 25 mM dATP; 1.5 μCi of [^{35}S] dATP; and 0.5 units of *Taq* DNA polymerase (Perkin-Elmer). Reaction samples were transferred to 96-well plates and were subjected to 35 cycles each consisting of denaturation for 30 s at 94°C; annealing for 30 s at temperatures varying from 55°C to 57°C, depending on the specificities of the oligonucleotide primers; and elongation for 30 s at 72°C.

PCR reaction products were electrophoresed on 6% denaturing polyacrylamide sequencing gels. Sizes of alleles were determined by use of an M13 phage vector sequence. Table 1 shows allele sizes determined for each of the five markers tested in the ACCPN candidate region.

Genetic Analysis

Two-point linkage analysis was performed by use of the MLINK program version 5.1 from the LINKAGE computer package (Lathrop et al. 1984). At any given locus, results for all ACCPN pedigrees were added, to obtain a final LOD score for the marker tested. Addition of the results was feasible because the disease is clinically homogeneous, the homogeneity being strengthened by

Table 2

Two-Point LOD Scores for Chromosome 15 Markers Spanning the ACCPN Candidate Region

	LOD SCORE AT RECOMBINATION FRACTION OF							
MARKER	0	.01	.05	.1	.15	.2	MAXIMUM LOD SCORE	RECOMBINATION FRACTION
D15S1040	−∞	11.02	10.18	8.61	6.98	5.41	11.02	.001
D15S971	11.1	10.79	9.55	8.02	6.53	5.12	11.1	0
D15S118	−∞	7.62	7.31	6.35	5.28	4.20	7.67	.017
D15S1012	−∞	−.09	2.21	2.67	2.57	2.24	2.67	.11
D15S214	−∞	1.88	3.74	3.84	3.47	2.91	3.89	.079

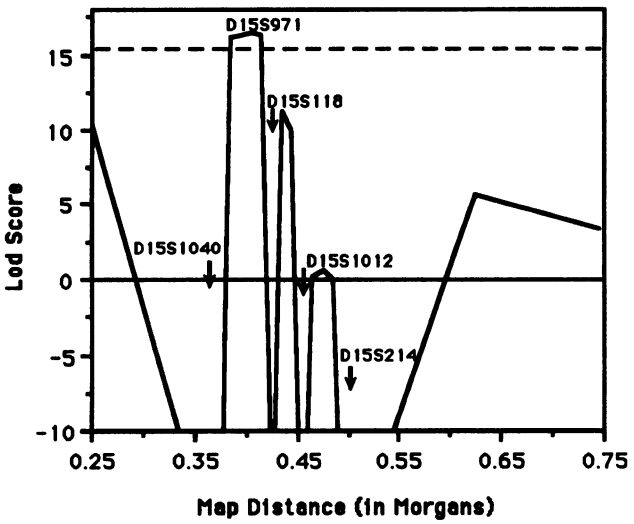

Figure 1 Multipoint linkage analysis for five chromosome 15q13-q15 markers spanning the ACCPN candidate region. Genetic distances between the markers were obtained from the most recent Généthon genetic map, created by use of the GMS algorithm (C. Dib, S. Fauré, C. Fizames, D. Samson, N. Drouot, A. Vignal, P. Millasseau, S. Marc, J. Hazan, E. Seboun, M. Lathrop, G. Gyapay, J. Morissette, and J. Weissenbach, unpublished data), and are as follows: D15S1040–D15S971 = 4 cM; D15S971–D15S118 = 1 cM; D15S118–D15S1012 = 3 cM; and D15S1012–D15S214 = 4 cM. The maximum LOD score obtained when all 14 families were combined was 16.435 adjacent to D15S971. The horizontal dashed line represents the maximum LOD score − 1.00.

evidence of a founder effect in this population. Precise values for maximum LOD score were calculated with the ILINK program from the same computer package.

LOD scores were generated on the basis of an autosomal recessive mode of inheritance for ACCPN with complete penetrance. The disease-gene frequency considered was 1/40 (Andermann 1981). Allele frequencies were established for five markers in the refined ACCPN candidate region, on the basis of a control group of 72–76 normal chromosomes from unrelated French Canadians from different regions of Quebec (table 1).

Sequential four-point linkage analysis was carried out by use of the LINKMAP program version 5.1 of the LINKAGE package (Lathrop et al. 1984). When necessary, alleles for the five markers spanning the ACCPN candidate region were recoded to lessen computing time (Ott 1991). Results from the four-point analyses were plotted contiguous to each other (Terwilliger and Ott 1994).

χ^2 and Fisher exact tests were performed in the investigation of linkage disequilibrium both at individual marker loci and with haplotypes. The degree of disequilibrium was determined by use of $\delta = (p_D - p_N)/(1 - p_N)$, where p_D and p_N represent the frequency of a particular associated allele on disease and control chromosomes, respectively (Risch et al. 1995). For individual loci, two strategies involving different case samples were employed. First, the ACCPN case sample comprised one randomly selected affected individual from each unrelated pedigree (48 affected chromosomes, including 12 unrelated single ACCPN cases not used in the linkage analysis). The other approach was to assess the disequilibrium in all affected chromosomes (94 in total). The control sample for these analyses was a group 76 normal chromosomes from 38 unrelated French Canadian individuals from different regions of Quebec. To assess linkage disequilibrium for haplotypes, all affected individuals from each of the 14 collected families (66 chromosomes) were compared with a control group comprising the unaffected chromosome of each parent (21 haplotypes).

Results

Preliminary Linkage Analysis

A genomewide search examining 120 markers identified linkage of ACCPN to chromosome 15 on the basis of an initial positive LOD score for marker D15S117. A total of 15 markers were tested on the long arm of chromosome 15 (data not shown), in order to define the smallest ACCPN candidate region. Table 2 shows the two-point LOD scores for five markers spanning the ACCPN candidate region. The highest LOD score, 11.1 (recombination fraction 0), was obtained with marker D15S971. Lod scores of all markers surpassed the standard criterion of 3, except that for marker D15S1012, which was uninformative in our families.

Refinement of the Candidate Region

Four-point linkage analysis gave a maximum LOD score of 16.43 centromeric to marker D15S971 (fig. 1). Odds ratios showed that the most probable localization for the ACCPN gene was within the 5-cM interval flanked by D15S1040 and D15S118. This region was 1.54×10^6 times more likely to encompass the disease-gene locus than was the region centromeric to D15S1040; 5.48×10^{10} times more likely than the region telomeric to D15S214 and was 933 times more likely to do so than was the region between D15S118 and D15S1012.

We constructed haplotypes for all 14 pedigrees, using the five markers in the ACCPN candidate region (data not shown). Recombination events in pedigrees ACCPN-1, ACCPN-2, ACCPN-3, and ACCPN-7 localized the ACCPN gene to a 5-cM region flanked by markers D15S1040 and D15S118 (fig. 2). One recombination (individual II-6 from ACCPN-3) mapped the ACCPN gene centromeric to D15S118. The centromeric boundary for ACCPN was defined by a recombination event in individual II-5 from family ACCPN-2.

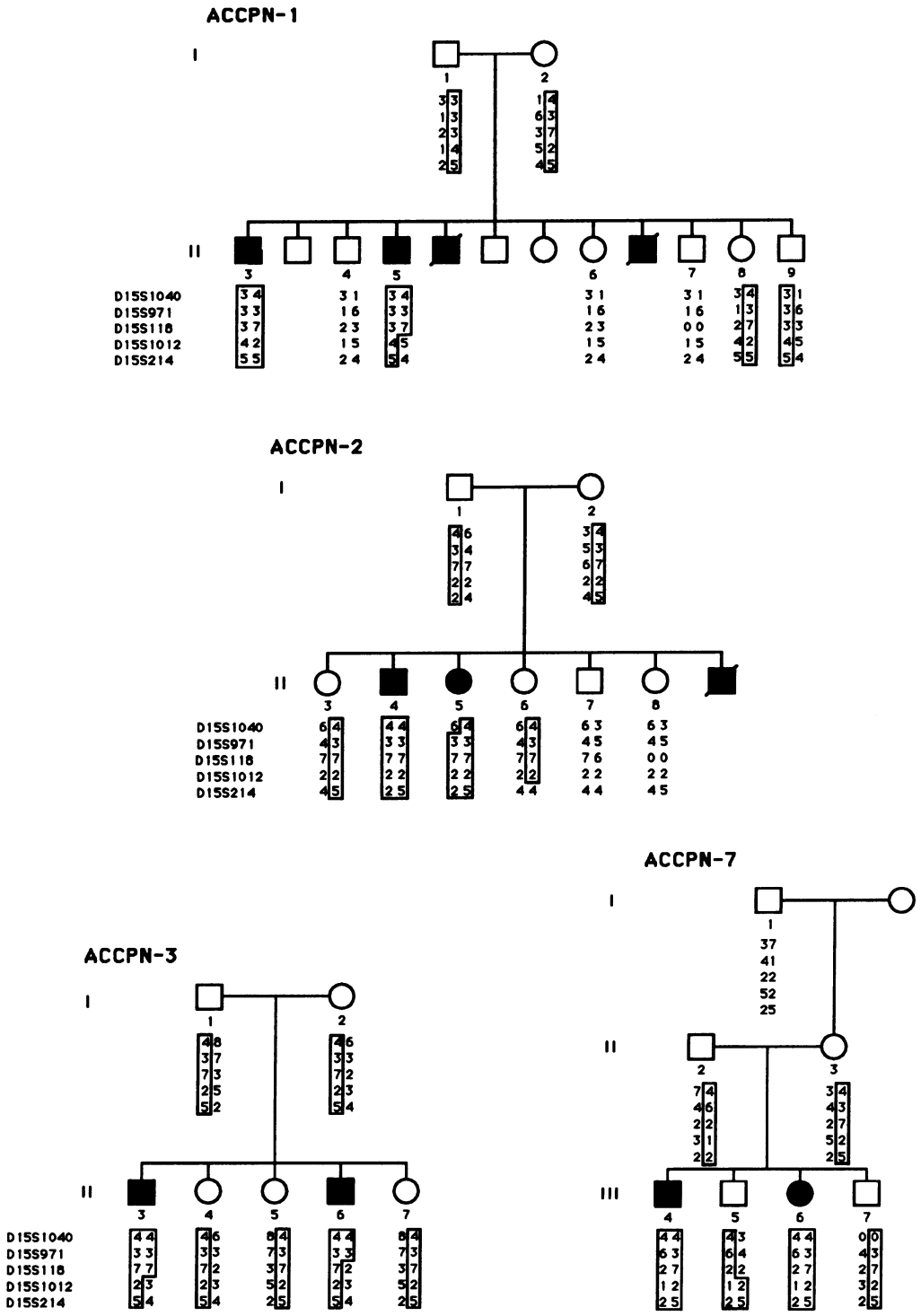

Figure 2 Haplotypes for four pedigrees included in the linkage analysis, which demonstrate important recombination events for narrowing the interval containing the ACCPN gene. Genetic markers are ordered from the centromere to the telomere. The haplotypes segregating with the disease in these kindreds are enclosed by boxes. Blackened symbols denote affected individuals. A diagonal line through a symbol denotes that the individual is deceased.

Table 3

Allelic Association between Five Chromosome 15 Markers and the ACCPN Gene

Marker and Sample Group[a]	Frequency of Allele[b]									p	δ[c]
	1	2	3	4	5	6	7	8	9		
D15S1040:											
A	...	...	.04	.92	...	.02	...	...	.02	4.88×10^{-18}	
B	...	...	.07	.90	...	.02	...	...	.01	9.99×10^{-16}	.882
Control	.01	.05	.35	.15	.07	.22	.03	.09	.03		
D15S971:											
A	...	...	.88	.06	...	.04	...	.02	...	2.47×10^{-13}	
B	...	...	.92	.03	...	.03	...	.01	...	9.99×10^{-16}	.902
Control	.01	.03	.18	.19	.07	.11	.35	.06	...		
D15S118:											
A	...	.08	.06	...	...	.02	.83	...	...	3.83×10^{-12}	
B	...	.06	.05	...	...	.02	.86	...	...	9.99×10^{-16}	.825
Control	.04	.27	.18	.04	.01	.22	.20	.03	.01		
D15S1012:											
A	.08	.67	.04	.06	.15	...	...	...	...	6.51×10^{-7}	
B	.08	.75	.04	.04	.09	...	...	...	...	7.99×10^{-12}	.679
Control	.20	.22	.32	.01	.19	.05	.01	...	...		
D15S214:											
A	...	.39	...	.18	.43	...	...	...	...	6.27×10^{-6}	
B	...	.42	.01	.14	.43	...	...	...	...	4.38×10^{-7}	
Control	.03	.57	.01	.31	.07	.01	...	...	...		

[a] Markers are ordered from centromere to telomere (top to bottom) in a 12-cM interval on chromosome 15q13-q15. Two sample groups were analyzed: in group A, one affected individual per family (44–48 chromosomes) was randomly selected; and in group B, all affected cases (88–94 chromosomes) were considered. The control sample comprised 72–76 normal chromosomes. δ Values were calculated for sample group B.

[b] Underlining denotes alleles found in excess in the ACCPN cases.

Identifying the Ancestral ACCPN Chromosome

The comparison between the frequency of alleles occurring in ACCPN chromosomes and that in normal control chromosomes is summarized in table 3. Significant linkage disequilibrium was observed in one particular allele for markers D15S1040, D15S971, D15S118, and D15S1012. When all affected cases were included, the locus with the highest proportion of ACCPN chromosomes carrying the same allele was D15S971, where 92% had allele 3. The DNA marker at the D15S214 locus showed no predominant allele in the sample of ACCPN patients; of the two alleles that were seen most frequently in ACCPN chromosomes (42% and 43% for alleles 2 and 5, respectively), allelic association was found with allele 5 (260 bp; $p = 4.38 \times 10^{-7}$) but not with allele 2 (251 bp; $p = .062$).

Examination of haplotypes of all affected individuals showed that the haplotype of markers D15S1040-D15S971-D15S118, haplotype 4-3-7, was seen in 79% of ACCPN chromosomes, as opposed to the situation in parental control chromosomes, where no similar haplotype was found ($p = 1.97 \times 10^{-16}$). By reducing the haplotype into two smaller intervals, D15S1040-D15S971 and D15S971-D15S118, a greater proportion of ACCPN chromosomes that shared a common haplotype was seen. The interval of D15S1040-D15S971, haplotype 4-3, comprised 85% of ACCPN chromosomes but was not found in the control chromosomes ($p = 8.58 \times 10^{-19}$). The second interval, of D15S971-D15S118, haplotype 3-7, comprised 88% of ACCPN chromosomes ($p = 4.43 \times 10^{-16}$) but was also seen in 6% of the normal control chromosomes.

Discussion

ACCPN is a relatively rare condition that primarily affects French Canadian populations. Agenesis of the corpus callosum (ACC) is a developmental disturbance that can occur with no obvious phenotype but often is found associated with inherited metabolic diseases and congenital malformations, such as Zellweger syndrome, nonketotic hyperglycinemia, and trisomies 8, 13, and 18 (Menkes et al. 1990). To date, little progress has been made in elucidating the causes of ACC and its role in these diseases. In one X-linked ACC disorder, Aicardi syndrome, a locus on chromosome Xp22.2 has been implicated (Donnenfeld et al. 1990; Lindsay et al. 1994). By mapping ACCPN, we have defined a new gene locus that may play a role in these developmental anomalies.

Also of interest is the severe axonal sensorimotor neuropathy always present in ACCPN cases, which is analogous to the hereditary motor and sensory neuropathies type 2 (HMSN2). One locus for HMSN2, or Charcot-Marie-Tooth type 2 (CMT2), has been identified on chromosome 1p36, but other CMT2 pedigrees do not show linkage to this region (Chance and Fischbeck 1994). Recently, a second locus for CMT2 has been identified on chromosome 3q in one large family (Kwon et al. 1995). All families reported to map to chromosome 1p or chromosome 3q show an autosomal dominant mode of inheritance. Among the autosomal recessive forms (CMT4), a locus on chromosome 8q was reported in families with CMT4 type A, which is characterized by hypomyelination in nerve biopsy (Ben Othmane et al. 1993). The ACCPN gene locus appears to be a novel locus that may give further evidence for the heterogeneity of HMSN.

The ACCPN gene was localized within the 5-cM interval flanked by D15S1040 and D15S118. Using the 1994 chromosome 15 consortium map (Malcolm and Dorion 1994), which places D15S118 relative to two physically assigned genes (8.1 cM telomeric to FMN on 15q13-q14 and 6.4 cM centromeric to THBS1 on 15q15), we can assign the ACCPN gene to 15q13-q15. Though several genes have been mapped to this chromosomal region, there are no candidate genes for ACCPN. Furthermore, no candidate genes map to mouse chromosome 7 (Rinchik 1992), which is homologous to 15q11-q13.

The ACCPN candidate region could be further reduced by identifying and assessing historical recombinants. The most conserved portion of the ancestral ACCPN chromosome encompasses markers D15S1040-D15S971-D15S118, where 79% of ACCPN patients have the same 4-3-7 haplotype. Although family ACCPN-7 (fig. 2), for example, transmits to affected individuals a disease chromosome, that has only conserved the very centromeric allele of the most common haplotype. This probable historical recombination between D15S1040 and D15S971 would place the ACCPN gene within this 4-cM region.

The combination of a malformation with a progressive neurological disease is highly unusual. In ACCPN, it appears likely that the fibers that begin to cross from hemisphere to hemisphere to form the corpus callosum are exposed to some factor, in the cerebrospinal fluid environment, that damages them, resulting in ACC (Carpenter 1994). It remains to be determined whether both abnormalities, the CNS malformation and the progressive neuropathy, are determined by the same abnormal gene or by abnormalities in two different genes, such as in a contiguous-gene deletion syndrome.

Localizing the ACCPN gene to 15q13-q15 has important implications for diagnostic testing in French Canadian families from the Charlevoix and Saguenay-Lac St Jean regions. This is significant because of the high (1/20) carrier frequency in this population. Also, information about the ACCPN gene may provide important genetic clues for other syndromes associated with either ACC or sensorimotor neuropathy and, in turn, may contribute to the general knowledge of the formation and development of the corpus callosum, as well as of the functions of related systems affected by ACCPN.

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